REMARKS

Reconsideration of this application is respectfully requested.

Claims 1-85 were presented for examination. Claims 1-40, 47-49, 52-65, and 74-77 were previously cancelled. Thus, claims 41-46, 50-51, 66-73, and 78-93 are presented for reconsideration.

Claims 43 and 45 were objected to under 37 CFR § 1.75(c), as being in improper dependent form for failing to further limit the subject matter of a previous claim. Applicant was required to cancel the claims, or amend the claims to place the claims in proper dependent form, or rewrite the claims in independent form. The Examiner stated that the recitation "the polynucleotide comprising the cPPT and CTS regions are derived from an HIV-type retrovirus" in claim 43 and the recitation "the cis-acting central initiation region (cPPT and the termination region (CTS) of an HIV-1 retroviral genome" in claim 45 do not further limit the phrase "wherein the cPPTand CTS are derived from a retrotransposon" in the base claim 41. Office Action at 2-3. This ground for rejection is respectfully traversed and reconsideration is requested for the following reasons.

With regard to the recitation of "a DNA sequence comprising the cis-acting central initiation region (cPPT) and the termination region (CTS) of an HIV-1 retroviral genome," claim 45 has been amended by deleting "retroviral genome." Thus, the claim now merely requires "a DNA sequence comprising the cis-acting central initiation region (cPPT) and termination region (CTS) of HIV-1." This recitation is now compatible with the recitation of "a retrotransposon" in base claim 41. Specifically, the "retrotransposon" of claim 41 could be other than "HIV-1." Thus, claim 45 limits the scope of claim 41 and is a proper dependent claim.

With regard to the recitation "a polynucleotide comprising the cPPT and CTS regions are derived from an HIV-1 type retrovirus" in claim 43, Applicant respectfully submits that this recitation is consistent with "a retrotransposon" in base claim 41. Specifically, while dependent claim 43 requires that the cPPT and CTS regions are derived from "an HIV-1 type retrovirus," the "retrotransposon" of base claim 41 could be other than an HIV-1 type retrovirus retrotransposon. Accordingly, claim 43 further limits claim 41 and is a proper dependent claim.

Claim 78 was objected to because of a typographical error in line 2 in the phrase "inside a protein envelope of the non-infectious practice." The Examiner suggested that Applicant replace the word "practice" with "particle." Office Action at 3. An appropriate correction has been made.

Claim 90 recites "POL," "GAG" and "ENV" polypeptides. According to the Examiner, the art-recognized nomenclature for a protein is the capitalized initial letter followed by non-capitalized two letters, for example, Pol, Env, Pro and Gag. Appropriate correction was required. Appropriate corrections have been made.

Applicant courteously submits that the foregoing amendments and remarks obviate each of the objections. Thus, reconsideration and withdrawal of the objections are requested.

Applicant acknowledges and thanks the Examiner for the withdrawal of the previous rejection of claims 41-46, 50,51 and 66-73 under 35 U.S.C. § 103(a) as being obvious over Verma et al (WO97/12622), Charneau et al. ('92), and Charneau et al. ('94). Office Action at 5. Applicant agrees with the Examiner's conclusion that these references, alone or in combination, do not render Applicant's claims obvious.

Concerning the provisional obviousness double-patenting rejection of Claims 41-45, 51, 66-70, 73, 78-85, and 90-93 because of Claims 36, 39, 41, 43-45, 52 and 69-73 of co-pending application No. 10/313,038, Office Action at 3-4, Applicant respectfully requests that this ground of rejection be held in abeyance pending an indication of allowable claims in one of these applications.

Applicant also acknowledges the Examiner's new ground of rejection under 35 U.S.C. § 103(a) over Verma, Charneau '92, and Charneau '94, and the newly cited Giovannangeli *et al.* publication. This ground for rejection is respectfully traversed.

The Examiner contends that Verma discloses a recombinant, non-replicative, non-infectious retroviral transfer vector comprising: (1) a transgene encoding luciferase or β-galactosidase, and (2) retroviral regulatory signals, HIV-1 LTR and RRE. The Examiner further contends that Verma discloses two additional vectors, a packaging construct comprising HIV Gag, Pol, Vif, Tat, Rev, and Nef, and a pseudotyping MLV vector. The Examiner acknowledges that the Verma retroviral transfer vector does not comprise cPPT and CTS. Office Action at 6.

According to the Examiner, Charneau '94 discloses that cPPT is an important cis-acting sequence for initiating DNA transcription by priming DNA synthesis. The Examiner contends that Charneau '94 further discloses a cis-acting HIV-1 CTS that is essential for terminating DNA synthesis by displacing the completed DNA strand, and Charneau '94 specifically discloses the nucleotide sequence of HIV-1 CTS. The Examiner recognizes that Charneau '94 does not disclose the nucleotide sequence of cPPT. Office Action at 6-7.

Charneau '92 was cited because it discloses the nucleotide sequence of HIV-1 cPPT. According to the Examiner, Charneau '92 also discloses that cPPT is an important sequence for initiating DNA transcription. Office Action at 7.

Applicant respectfully transverses this ground for rejection and requests reconsideration for the following reasons.

The Examiner acknowledged that claims 41-46, 50, 51, 66-73, 75-85, and 90-93 relate to a recombinant, non-replicative, non-infectious, lentiviral vector deprived of functional genes encoding lentiviral Gag, Pol, and Env proteins, and that the lentiviral vector comprises a polynucleotide comprising a cis-acting central polypurine tract ("cPPT") and a cis-acting central terminator sequence ("CTS"); a defined nucleotide sequence; and regulatory signals for reverse transcription, expression, and encapsidation, wherein the regulatory signals are of retroviral or retroviral-like origin. Office Action at 5-6.

It should be apparent from Applicant's claims that Applicant's vector, and the other embodiments of the invention incorporating the vector, contain, among other things, two distinct elements:

(1) a polynucleotide for formation of a DNA triplex, and

(2) a defined nucleotide sequence, *e.g.*, a transgene or sequence of interest.

Applicant's claims also define the relationship between these two distinct elements: "[T]he DNA triplex transfers the defined nucleotide sequence into the nucleus of a cell." *See* claims 36, 52, and 69. A DNA triplex is essential in Applicant's invention. The vectors exhibit defective and transduction properties without it.

If the rejection is maintained, the Examiner is requested to acknowledged these elements and their relationship in Applicant's claims and to point out where they occur in the prior art.

Lentiviral DNA Synthesis By Reverse Transcription

The Examiner asserted that it would have been obvious "to modify the Verma retroviral transfer vector so as to insert the initiation signal, cPPT, and the termination signal, CTS, from the upstream plus stand of the HIV-1 genome, as taught by Charneau '92 and Charneau '94, upstream from the coding sequence of the transgene in the retroviral transfer vector taught by Verma." Office Action at 7-8. Applicant disagrees.

The process of reverse transcription, which converts the retroviral RNA genome into DNA, is complex. Most of the knowledge of the reverse transcription process stems from the studies of the Moloney Murine Leukemia Virus (MoMLV) and has been extrapolated as such for HIV. According to the Moloney model of reverse transcription, only one PPT (polypurine tract sequence) is required for the conversion of the RNA genome into DNA. Charneau's '91, '92, and '94 papers indicate the reverse transcription process is even more complex with a second central initiation of plus strand synthesis at the center of the genome governed by the cPPT sequence and a central termination sequence, which blocks a central strand displacement event leading to the formation of a three-stranded DNA structure called DNA Triplex or DNA Flap. But theses papers do not establish at all that the resulting DNA Flap structure is involved in HIV-1 genome nuclear import or that this mechanism is operative in the context of a heterologous vector DNA sequence. Rather, at that time, the two additional central steps (initiation at the cPPT and termination at the CTS) in the reverse transcription process of HIV-1 and other lentiviruses was considered of marginal interest in the HIV-1

replicative cycle, since a single PPT sequence is enough to achieve the conversion of the RNA genome into DNA.

The Zennou et al., 2000 paper (and corresponding disclosure in U.S. Application No. 09/688,990, filed on October 17, 2000, now U.S. Patent 6,682,990) marked a clear-cut and definitive turning-point in the design of lentiviral vectors. Prior to Zennou et al., 2000, no described lentiviral vector system included the DNA Flap sequence (Sodroski 1991, HIV-1 derived vector; Naldini 1996, HIV-1 derived vector; Poeschla 1998, FIV derived vector; Olsen 1998, EIAV derived vector). In stark contrast, all lentiviral vectors described after Zennou et al., 2000 include the DNA flap sequence (Matukonis 2002, BIV derived vector; Mangeot 2000, SIV derived vector). Similarly, among the hundreds of publications originating from a large number of laboratories, which reported using lentiviral vectors for various purposes before Zennou et al., 2000, not one included the DNA Flap sequence. But for several years now, since the Zennou et al. 2000 paper, virtually all publications involving lentiviral vector have included the DNA Flap sequence.

It is, therefore, an indisputable fact that the demonstration in Zennou et al., 2000 that the DNA Flap is operative in a hererologous vector sequence context underlines the "failure of others to solve the problem." It stands to reason that this failure to solve the problem prior to Zennou et al., 2000 stemmed from an inability to identify the molecular nature of the problem, namely, the incapacity of the vector genome to cross the nuclear membrane of non-dividing cells, due to the lack of an appropriate experimental assay to address the issue. The Zennou et al. publication not only identified the problem, but provided the solution to the poor transduction efficiency of previous lentiviral vectors.

Lentiviral vector technology represents a technological breakthrough in the gene transfer field because it solves the problem of stable and efficient gene transfer in non-dividing target cells, such as neurons, hematopoietic stem cells, hepatocytes, and dendritic cells. This property entirely relies on the ability of the vector DNA genome to cross the nuclear membrane in order to access and integrate into the interphasic cell chromatin. This key step of mitosis-independent HIV-1 infection or vector transduction is called active nuclear import. Conversely, classical retroviral vectors deriving from onco-retroviruses, such as Moloney Mouse Leukemia Virus (MoMLV), are strictly dependent on cell mitosis for transduction, just as their parental viruses are mitosis-dependent for infection.

For the generation of efficient mitosis-independent lentiviral gene transfer vectors, it is therefore essential to include in the vector recombinant system all the lentiviral virus determinants of active nuclear import. The involvement of the DNA Flap sequence in this active nuclear import was wholly unpredictable. This mechanism of nuclear import involving a three-stranded DNA structure has no cellular or viral counterpart, and therefore, no one could have predicted that this unusual structure would have been operative in a nuclear import process. In fact, at that time of this invention, the extrapolation of the classical cellular mechanism for the nuclear import of cellular proteins to the HIV-1 virus led to the proposal that HIV-1 proteins that included potential nuclear localization signal, such as Matrix (MA) (Bukrinsky et al, Nature 1993), Vpr (Bukrinsky et al, PNAS1993), or Integrase (IN) (Gallay et al, PNAS 1997), were the actors of HIV-1 active nuclear import. These notions have subsequently been largely contradicted.

The design of the first generations of lentiviral vectors was directly inherited from the design of MoMLV vectors in which the entire coding sequences were deleted (GAG, POL, and ENV) to be replaced by the sequence of interest. By doing this, and without knowing it, researchers were deleting the central portion of HIV-1 genome, which includes the cPPT and the CTS sequences responsible for the formation of the DNA Flap during reverse transcription.

It stands to reason that the scientific community did not realize that a major step in the efficiency of gene transfer using lentiviral vector was still to be achieved because first generations of HIV-1 derived vectors were able to transduce genes in non-dividing cells, albeit with low titer (indicating that a small portion of vector genomes are imported in the nucleus using a DNA Flap independent pathway), and those vectors were presented as "perfectly efficient". In fact, no quantitative assay for retroviral DNA nuclear import was available at the time (only PCR on 2-LTR DNA circles), and researchers could, therefore, not realize that first generations of vectors lacking the central DNA Flap were exhibiting a strong nuclear import defect. All quantitative nuclear import assays for retroviral DNA originate from Dr. Charneau's lab, and Figure 6 of the Zennou et al. Cell 2000 paper not only represents the first quantitative demonstration of the stimulation to wild type levels of the nuclear import of a heterologous vector sequence by the DNA Flap sequence, but also establishes the rate of the nuclear import of the HIV-virus itself.

The Examiner stated that

> Charneau '94 describes that cPPT is an important cis-acting sequence for initiating DNA transcription by priming DNA synthesis . . . . Charneau '94 further describes a cis-acting

> HIV-1 CTS is essential for terminating DNA synthesis by displacing the completed DNA strand.

Office Action at 6. But these functions, together with the PPT, which the Examiner does not even mention, function to achieve viral DNA synthesis from viral RNA by reverse transcription. The Examiner has not explained how these reverse transcription mechanisms associated with cPPT and CTS sequences in lentiviral replication translate to Applicant's vector. The Examiner is requested to provide an explanation if the rejection is maintained.

Verma, Charneau '92, and Charneau '94

The Examiner attempts to justify the assertion of obviousness by stating that "[t]he skilled artisan would have been motivated to do so to improve the transfer, integration and sustained long-term expression of the transgene in the cell. Office Action at 8; emphasis added.) Applicant disagrees.

To reject a claim based on combining prior art elements according to known methods to yield predictable results, as the Examiner has done, Office personnel must articulate, among other things, a finding that, in combination, each element merely performs the same function as it does separately and a finding that one of ordinary skill in the art would have recognized that the results of the combination were predictable. MPEP 2143A. The stated basis for rejection Applicant's claims fails to fulfill these requirements.

The Office's statement that transfer of the transgene in the cell would be improved is unsupported in the record. Here, there are no findings that Verma, Charneau '92, or Charneau '94 show that a DNA triplex is responsible for transfer of nucleic acid, much less a transgene, into a cell, or that Applicant's claimed elements

perform the same function in combination as they do separately, or that the results would have been predictable. Applicant courteously refers the Examiner to the discussion of lentiviral DNA synthesis by reverse transcription, *supra*. If the rejection is maintained, the Examiner is requested to provide findings of fact by citing to facts in the record to support the assertion that transfer of the transgene would be improved by incorporating the cPPT and CTS sequences in Applicant's vector.

Similarly, the Examiner's statement that integration of the transgene would be improved is unsupported in the record. There are no findings of fact that Verma, Charneau '92, or Charneau '94 show that a DNA triplex causes integration of nucleic acids or a transgene into a cell, or that Applicant's claimed elements perform the same function in combination as they do separately, or that the results would have been predictable. Once again, Applicant refers the Examiner to the discussion, *supra*. If the rejection is not withdrawn, the Examiner is requested to provide findings of fact by citing to facts in the record to support the assertion that integration of the transgene would be improved by incorporating the cPPT and CTS sequences in Applicant's vector.

And finally, the Examiner's statement that it would have been obvious to insert the triplex sequence upstream of the coding sequence of the transgene "to improve the . . . sustained long-term expression of the transgene inside a cell" is unsupported by the record. Office Action at 7-8. There are no findings of fact or explanation of how an initiation sequence and a termination sequence upstream of the transgene will improve sustained long-term expression of the transgene inside the cell. The Examiner is requested to provide findings of fact to support the assertion that sustained, long-term

expression of the transgene would be improved by incorporating the cPPT and CTS sequences upstream of the coding sequence of the transgene in Applicant's vector.

The § 103 rejection should be withdrawn for the further reason that the Examiner has failed to make any findings of fact that Applicant's vector would have the replication and cell transduction properties recited in the claims if "the initiation signal, cPPT, and the termination signals, CTS, . . . [were inserted] upstream [of] the coding sequence of the transgene" as alleged in the Office Action. In other words, a factual basis for the assertion is lacking.

In summary, the inventors discovered that nuclear import by a lentivirus is dependent on the DNA triplex. Moreover, they discovered that the DNA triplex is able to function in vectors, out of the natural context of the lentiviral genome, as a nuclear import determinant enabling the vector genome to enter the nucleus of target cells. The inventors introduced the nucleotides that form this DNA triplex into a viral vector system containing a transgene and showed that transduction of the viral vector into the cells is increased by stimulating the amount of nuclear import of the vector DNA.

The implication of the DNA triplex in the nuclear import mechanism had never been recognized prior to Applicant's invention. There were no previous reports of nuclear import by a retroviral DNA triplex in viral or cellular systems. Consequently, this mechanism of nuclear import and the role of the DNA triplex was completely unpredictable. By no means was this discovery obvious at the time of Applicant's invention. For these reasons, a *prima facie* case of obviousness has not been made and the § 103 rejection should be withdrawn.

Giovannangeli

The Examiner asserted that:

> . . . Giovannangeli discloses that a triplex-forming oligonucleotide, directed against the HIV-1 polypurine tract (PPT), can specifically recognize and bind its 15bp target located on nuclear DNA involved in the intact supranucleosomal structure of chromatin (page 79, right column, middle paragraph). The targeted PPT sequence is located in the coding region of the pol gene but it belongs to a 500 bp fragment which has been shown to exhibit transcription enhancing activity and to contain several transcription factor binding sites. Such a region associated with regulatory functions is generally distinguished from the bulk chromatin by an increased accessibility of DNA to regulatory proteins and therefore appears also accessible to triplex-forming oligonucleotides (see the paragraphs bridging page 81 and 82). Therefore, this PPT is the recited cPPT in the instant claims and provides the evidence that the cPPT is a target site for DNA triplex formation.
>
> It would have been obvious to one ordinary skill in the art at the time the invention was made to modify Verma retroviral transfer vector so as to insert the initiation signal, cPPT, and the termination signal, CTS, from the upstream plus strand of HIV-1 genome, as taught by Charneau '92 and Charneau '94 , upstream from the coding sequence of the transgene in the retroviral transfer vector taught by Verma et al The skilled artisan would have been motivated to do so to improve transfer, integration and sustained long-term expression of the transgene inside a cell.

Office Action at 7-8.

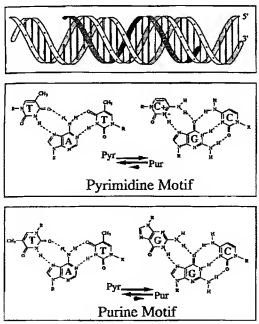
Applicant wishes to clarify the meaning of the term "triplex" in the invention, which is different from the concept of three-stranded DNA also known as a "triple-helical structure" or "triplex" in Giovannangeli. The Giovannangeli publication, in which the inventor, Dr. Charneau, was a contributor, describes the possibility of an oligonucleotide coupled with a photo-activable psoralen entity to recognize a 15-bp chromatin sequence

for inducing an adduct after UV irradiation of the cell. Giovannangeli's "triple-helical structure" is totally different from the "triplex" in Applicant's invention.

Triple Helix Formation by Hoogsteen Bonding

Nucleic acids can be selectively recognized by a large number of natural and synthetic ligands. Oligonucleotides provide the highest specificity of recognition. They can bind to a complementary single-stranded sequence by forming Watson-Crick hydrogen bonds. They can also recognize the major groove of double-helical DNA at specific sequences by forming Hoogsteen or reverse Hoogsteen hydrogen bonds with purine bases of the Watson-Crick base pairs, resulting in a triple helix. Triple-helix formation through oligonucleotide binding to DNA is a sequence-specific interaction involving primarily homopurine-homopyrimidine sequences in the double-helical target.

The following Figure depicts the pyrimidine motif for triple-helix formation and the purine motif for triple helix formation.



The bound oligonucleotide is located in the major groove of DNA, bound by sequence-specific hydrogen bonding to the bases of the purine strand in the Watson-Crick duplex. Parallel Hoogsteen hydrogen bonding (pyrimidine motif) or antiparallel, reverse Hoogsteen hydrogen bonding (purine motif) is involved. Base triplets and strand orientations are depicted in the figure. Ex. 1 at pg. 69.

Applicant provides this background explanation because Giovannangeli describes a triple-helical structure involving Hoogsteen bonding. Giovannangeli demonstrated that a triplex-forming oligonucleotide, directed against the HIV-1 polypurine tract, can specifically recognize and bind its 15 bp target located on nuclear DNA. The authors used an oligonucleotide-psoralen conjugate as a tool to trap the triple-helical complex formed in the cell nucleus. Photochemical reaction of psoralen with the DNA strands at the triplex site converted a noncovalent triplex into a covalent one and resulted in a localized damage on genomic DNA. Giovannangeli at pg. 79.

Effect of Triple Helix on Gene Expression

The formation of a triple-helical structure arising from the Hoogsteen bonding of an oligonucleotide to a specific sequence on a Watson-Crick double helix can affect gene expression in several ways:

1) The triplex-forming oligonucleotide can overlap the recognition and binding sites of one of the components of the transcription or replication machinery. Competition for binding to the same site is expected to exert a direct effect on the biological process. (See Fig. 15 b, d, e of Ex. 2 at pg. 685).

2) The DNA conformational change, which has been demonstrated to occur upon triplex formation, may perturb the binding of protein factors and/or enzymes. The

perturbation of the double helix extends outside the oligonucleotide binding site, and medium-range effects on protein binding can therefore be expected. Long-range effects may also occur due to triplex-induced bending, change in bending and/or stiffening of the DNA double helix. The types of conformational perturbations might alter through-space interactions between, for example, two transcription factors bound to different regions of the DNA or may modify the distribution of nucleosomes within the chromatin structure. (See Fig. 15a, c of Ex. 2 at pg. 685).

3) A triplex-forming oligonucleotide bound immediately downstream of RNA polymerase attached to its promoter site might prevent initiation of transcription. Inhibition might also occur when an oligonucleotide binds close enough to DNA polymerase at an origin of replication. (See Fig. 15f of Ex. 2 at pg. 685).

4) An oligonucleotide bound to DNA might act as a "roadblock" for the transcription or replication enzymes. (See Fig. 15g of Ex. 2 at pg. 685).

One would have expected, therefore, that Giovannangeli's triple-helical structure involving Hoogsteen bonding would inhibit DNA transcription

Comparison of the Triple-Helical Structure with the Triplex of the Invention

In order to assist the Examiner in discerning the profound differences between the triplex, which forms part of Applicant's invention, and Giovannangeli's triple-helical structure formed by Hoogsteen bonding of an oligonucleotide with Watson-Crick base pairs, Applicant submits the following additional remarks.

First, the cPPT sequence in Giovannangeli was chosen only because its A/G-rich sequence is compatible with triple helix formation by Hoogsteen pairing. Any other cellular A/G–rich sequence would have been adequate for this study. Nevertheless, the

use of an appropriate artificial oligonucleotide is essential in Giovannangeli's protocol. The Examiner has not provided any explanation or reasoning to support the apparent belief that it would have been obvious to utilize a similar artificial oligonucleotide in Applicant's invention. Giovannangeli's oligonucleotide is a 15-mer of a sequence, which is not present in the displaced strand of the DNA Flap structure. It cannot, therefore, be compared with the natural DNA Flap structure in the center of the unintegrated HIV-1 linear DNA, precursor of the integrated provirus. Clearly, the authors do not suggest or even imply that the cPPT sequence might have a particularly surprising and beneficial effect in a transfer vector.

Second, the recognition by Giovannangeli's artificial oligonucleotide involves the formation of a triple helix by Hoogsteen base pairing within the large groove of the target cellular DNA. See the right panel of Appendix A, attached hereto. This triple-helix is structurally different from the HIV-1 DNA Flap, also called "triplex" in the invention, because of the presence of three DNA strands. See the left panel of Appendix A. Hoogsteen base pairing involving an artificial oligonucleotide leading to a genuine triple-helix is not involved in Applicant's invention.

In addition, the DNA Flap is characterized by a displaced strand, which does not contain the cPPT (central polypurine tract) sequence. The displaced strand is situated downstream of the cPPT. See the panels of Appendix A. The displaced strand of the DNA Flap is free from interactions with the upstream duplex. Appendix A. It is not at all a genuine triple-helical structure like the one formed by Giovannangeli's artificial oligonucleotide. It is a three-stranded DNA structure. These substantial differences in overall structure are not addressed in the Office Action.

Third, Giovannangeli's artificial oligonucleotide coupled with a photo-activatable psoralen was transfected in chronically HIV-1 infected cells containing an integrated HIV-1 provirus. It is important to know that, at this stage, the DNA Flap structure does not exist anymore. The DNA Flap is repaired by the cellular DNA repair machinery, allowing transcription of the viral DNA, and thus is converted into a classical Watson-Crick DNA helix. The Examiner stated that: "Neither Charneau '94 or Charneau '92 describe the formation of a DNA triplex" as recited in Applicant's claims. Office Action at 7. To contend that Giovannangeli describes the triplex in Applicant's claims misapprends the teachings of this reference.

Fourth, the consequence of triple-helix formation after pairing of Giovannangeli's oligonucleotide and UV irradiation is an inhibition of the transcription of the provirus. Nevertheless, the Examiner contends that it would have been obvious to combine the cited art, including the Giovannangeli reference, "to improve ... sustained long-term expression of the transgene inside a cell." Office Action at 8. The Examiner has not provided any explanation of why Giovannangeli's triple helical structure would improve expression of a transgene inside a cell. The Examiner's contention is in direct conflict with the facts of record.

Fifth, the Examiner contends that it would have been obvious to combine Giovannangeli with the other cited references "to improve the transfer ... of the transgene inside a cell." *Id.* The stage targeted by the modified oligonucleotide strategy disclosed by Giovannangeli, however, occurs after nuclear import in the HIV-1 replicative cycle. The Examiner has not provided any explanation of why Giovannangeli's triple helical structure, formed after viral transfer, would improve

transfer of a transgene into a cell. The Examiner's contention is unsupported by the facts of record.

Sixth, the Examiner contends that it would have been obvious to combine Giovannangeli with the other cited references "to improve ... integration ... of the transgene inside a cell." *Id.* Once again, the Examiner's contention is inconsistent with the facts of record. The artificial oligonucleotide strategy disclosed by Giovannangeli, targets the Watson-Crick sequence after integration of the viral RNA in the HIV-1 replicative cycle.

And finally, the Examiner concluded that it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify Verma's retroviral transfer vector so as to insert the initiation signal, cPPT, and the termination signal, CTS, as taught by Charneau '92 and Charneau '94, upstream from the coding sequence of the transgene in the vector taught by Verma et al. Office Acton at 7-8. Withdrawal of the earlier rejection based on Verma, Charneau '92, and Charneau '94 confirm Applicant's belief and the Examiner's conclusion that Applicant's claims are not rendered obvious by these three references. The Examiner has not provided any explanation of how the teachings of Giovannangeli remedy the deficiencies in the other three reference. Applicant submits that Giovannangeli could not possibly support this conclusion in view of the differences between Giovannangeli's triple-helical structure and Applicant's triplex.

In conclusion, one of ordinary skill in the art would never have thought to combine the information disclosed in the Giovannangeli paper with the teachings of Verma, Charneau '92, and Charneau '94 to design the transfer vectors claimed by

Applicant. Accordingly, Applicant submits that the rejection under § 103(a) should be withdrawn.

Please grant any additional extensions of time required to enter the attached reply and charge any additional required fees to Deposit Account 06-0916.

Respectfully submitted,

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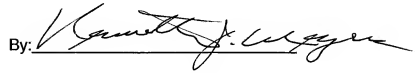
GARRETT & DUNNER, L.L.P.

Dated: August 12, 2009

By: 

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